DETAILED ACTION

Status of Action

The Examiner acknowledges receipt of application number 11/768,860 filed on 09/05/2006. Claims 1-20 are pending in this application.

In claim 5, please note the typographical error "**as**' should be corrected.

In claim 9, please note the typographical error "microcristalline".

Status of Claims

Accordingly, claims 1-20 are presented for examination on the merits for patentability.

Claim Rejections - 35 USC § 112 second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 5-7, 9-11, 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. All dependent claims are also included in this rejection.

(**1**) **Claim 5** recites the modified release granules comprises at least one polymer selected from.....and methylcellulose, which is indefinite because the species of the polymer is written in an improper Markush format "selected from...and" (see claims at page 32). Although alternative claim expressions using Markush format are permitted, they must present no uncertainty or ambiguity with respect to the question of scope or clarity of the claims.

In the instance case, claim 3 is written in Markush format **without** the transitional phrase "**consisting of**", are considered indefinite because it is unclear whether the claims should be read to include other additional, unrecited elements or not. Since one of ordinary skill in the art would not be reasonably apprised of the scope of the claims, therefore, the claims are rendered indefinite. It is suggested that the phrase "**selected from the group consisting of...and...**" be adopted.

(**2**) **Claims 9-10** recites the component "microcrystalline cellulose", which lacks sufficient antecedent basis because the precedent claim 1 does not recite this component.

Likewise, claim 10 recites the component "at least one natural starch as disintegrant", which also lacks sufficient basis because the precedent claim 1 does not recite this component.

(**3**) **Claim 19** provides for the use of the compound 10, 11-dihydro-10-hydroxy-5H-dibenz[b, f]azepine 5-carboxamide, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where

it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejection - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim **19** provides for the use of 10, 11-dihydro-10-hydroxy-5H-dibenz[b, f]azepine 5-carboxamide, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 19 is rejected under 35 U.S.C. 101 because the claimed recitation of a **use**, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 8, 12-13, 15, 18-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Volosov et al. (WO 00/01416).

Volosov et al. discloses pharmaceutical compositions for oral administration, which exhibit controlled drug release and the compositions are preferably applied as tablets or micro-particulate systems. (see page 1: Field of Invention).

More specifically, Volosov et al. discloses that the pharmaceutical compositions comprises monohydroxycarbazepine (MHD, licarbazepine) in combination with the lipophilic waxes WITEPSOL® and/or MYVACET® (p. 15 - 16). 400 mg of active ingredient was combined with 15 – 28 % by weight of wax so more than half (about 72 – 85 %) of the weight of the tablets was licarbazepine. This dosage form is capable of being adapted to a once a day administration.

The release of the drug under the conditions claimed by Applicant in claims 12 and 13 is not disclosed by Volosov et al. However, in figure 19, the plasma concentrations of MHD over an 11 hour time span shows a controlled release of the drug over this time period, indicating that it is likely that 70 - 90% or 80 - 90% of the drug is released within 8 – 12 hours under the conditions recited by Applicant. It is noted that In re Best (195 USPQ 430) and In re

Fitzgerald (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second column, first full paragraph).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

(1) Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Volosov et al. (WO/01416) in view of Beydoun et al. (Expert Opin Pharmacother 2002).

Applicants Claim

Applicants claim a method for the treatment of affective comprising orally administering to a patient in need of 10, 11-dihydro-10-hydroxy-5H-dibenz[b, f]azepine 5-carboxamide once a day. It should be noted that 10, 11-dihydro-10-hydroxy-5H-dibenz[b, f]azepine 5-carboxamide is also commonly known as licarbazepine.

Determination of the scope and content of the prior art

(MPEP 2141.01)

Volosov et al. teaches pharmaceutical compositions for oral administration, which exhibit controlled drug release and the compositions are preferably applied as tablets or micro-particulate systems. (see page 1: Field of Invention).

More specifically, Volosov et al. teaches that the pharmaceutical compositions comprises monohydroxycarbazepine (MHD, licarbazepine) in combination with the lipophilic waxes WITEPSOL® and/or MYVACET® (p 15 - 16). 400 mg of active ingredient was combined with 15 – 28 % by weight of wax so more than half (about 72 – 85 %) of the weight of the tablets was licarbazepine. This dosage form is capable of being adapted to a once a day administration.

The release of the drug under the conditions claimed by Applicant in claims 12 and 13 is not disclosed by Volosov et al. However, in figure 19, the plasma concentrations of MHD over an 11 hour time span shows a controlled release of the drug over this time period, indicating that it is likely that 70 - 90% or 80 - 90% of the drug is released within 8 – 12 hours under the conditions recited by Applicant. It is noted that In re Best (195 USPQ 430) and In re Fitzgerald (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second column, first full paragraph).

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Volosov et al. does not exemplify the treatment of individuals with affective disorders. However, the deficiency is cured by Beydoun et al.

Beydoun et al. discloses the oxcarbazepine (OXC) is rapidly reduced by cytolsolic enzymes to MHD, which is the substance responsible for the pharmacological effects of OXC such as its anticonvulsant activity (p. 60, col. 1). Administration of OXC for the treatment of bipolar disorder, identified by

Applicant as an affective disorder on p. 8 of the instant specification has been investigated (p. 66, Section 4.3 and 4.3.1).

Finding of prima facie obviousness Rational and Motivation

(MPEP 2142-2143)

It would have been obvious to a person of ordinary skilled in the art at the time the invention was made to combine the teaching of Volosov et al. and Beydoun et al. to arrive at the instant invention.

One of ordinary skill in the art would have been motivated to take the controlled release dosage form of licarbazepine and administer the dosage form once per day for the treatment of the affective disorder, bipolar disorder, as OXC is rapidly converted to licarbapezine, in which its use is known in the art as disclosed by Beydoun et al.

Therefore, from the teaching of the references, the invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference.

(2) Claims 1-2, 4-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Katzhendler et al. (US 6,296,873) in view of Gorham et al. (U. S. Patent Application Publication No. 2005/0214388) and Thombre, A. G. (U. S. Patent Application Publication No. 2003/0175326) combined.

Applicants Claim

Applicants claim a pharmaceutical oral controlled release composition comprising 10, 11-dihydro-10-hydroxy-5H-dibenz[b, f]azepine 5-carboxamide; at least one polymer, i.e. ethyl cellulose and polymethacrylates, as retarding agents. It should be noted that 10, 11-dihydro-10-hydroxy-5H-dibenz[b, f]azepine 5-carboxamide is also commonly known as licarbazepine.

Determination of the scope and content of the prior art

(MPEP 2141.01)

Katzhendler et al. teach a zero-order sustained release delivery system for carbamazepine or derivatives thereof (abstract). Specifically mentioned is 10, 11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide (licarbazepine, col 6, ln 44- 45). The amount of drug present ranges from about 100 mg to about 1200 mg per tablet (col 8, ln 19 - 20). The second component of the delivery system is at least one hydrophilic polymer that when hydrated, forms a gel (col 8, ln 23 - 27). HPMC is particularly preferred for use with carbamazepine derivatives because of the very low water solubility of the active ingredient (col 8, ln 55 - 57). Also because of the low water solubility of the active ingredients, it is advantageous to reduce the particle size using a process such as milling to a fine powder, to control the release kinetics and enhance solubility (col 10, ln 55 - 59). The viscosity of the polymer controls the release rate of the drug (col 8, ln 57 - 65). A daily dose can be formulated in a single tablet or more than one tablet, depending on the daily dose and number of time the formulation is to be administered (col 11, ln 26 - 30). The formulation of the instant invention can be

delivered once or twice per day (col 11, ln 31 - 32). Figures 7 - 10 and 12 - 15 show the release over time of carbazepine from formulations with varying amounts and viscosities of HPMC and optional additives. Increasing the concentration of METHOCEL® (HPMC) increases the viscosity and strength of the gel layer, resulting in a decreased erosion rate of the table (col 16, ln 20 - 23).

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Katzhendler et al. does not explicitly prepare a dosage form of MHD with other polymer and excipients, as claimed. However, the deficiencies are cured by Gorham et al. and Thombre, A. G.

Gorham et al. teach an oral controlled release dosage forms, i.e. a tablet, for therapeutic purposes. Gorham et al. teach that controlled release portion of a dosage form can be formulated and constructed using a common controlled release dosage form that results in a desirable controlled rate of release of the therapeutic agent. An advantage of a controlled release dosage form is that relatively high local concentration of the active in the gastrointestinal tract are avoided, due to a controlled, gradual distribution of the active throughout the gastrointestinal tract, preferably starting in the stomach (page 5: [0048]).

Gorham et al. also teach that various different types of controlled release dosage forms may be useful. Typically, a controlled release dosage form can

include therapeutic magnesium in combination with one or more additional pharmaceutically acceptable ingredients such as a binder, a controlled release agent, or a coating (e.g., a water-insoluble coating). A controlled release agent can be used to control the rate of release of an active ingredient, e.g., by slowing dissolution of a dosage form or a portion thereof. A coating can be used also to control or moderate release of an active ingredient, generally by requiring the coating to be dissolved before active ingredient is released from a coated portion of a dosage form such as a particle. The controlled release dosage form may include any of these components structured in a useful controlled-release form, such as in the form of a compressed tablet, etc., as desired (page 6: [0049]).

Gorham et al. further exemplify the useful excipients for use in dosage form, e.g., for holding together a particle, a compressed tablet include microcrystalline cellulose, hydroxypropyl methylcellulose, starches, lactose, sucrose, mannitol, sorbitol, polyvinylpyrrolidone, methylcellulose, ethyl cellulose (page 6: [0050]).

Gorham et al. then teach that controlled release agents are ingredients known in the pharmaceutical art, which can be added to a dosage form such as a compressed tablet or particle, to control release of an active ingredient. For example, a controlled release agent present in combination with a binder and therapeutic magnesium can slow the speed of erosion of the binder, thereby causing a slow and gradual erosion of a compressed dosage form and a gradual release of therapeutic active. Examples of useful controlled release agents (or

"sustained" release agents) include generally water-soluble polymeric materials such as hydrophilic cellulosic compounds including high viscosity hydroxypropyl methylcellulose (e.g., Methocel K100 MCR from Dow), methyl cellulose; polymethacrylates (e.g., Eudragit RL and RS from Degussa); ethyl cellulose; and combinations of these or others. The compressed dosage forms may also optionally include other non-active ingredients: a disintegrant such as a modified starch (page 6: [0051-0053]).

Thombre, A. G. teaches a chewable controlled release pharmaceutical composition, in which Thombre, A. G. teach that the controlled release composition is for oral administration (page 2: [0013]).

Thombre, A. G. also teach that the pharmaceutically active agent can be prepared into the formulation as form of particles having an average particle size up to 5000 μm (page 2: [0014]). Thombre, A. G. then teach that the use of coatings for the dosage form is preferred, wherein the coating formulation can be delayed release or sustained release type of coatings prepared by the usable polymers, i.e. hydroxypropyl-methylcellulose, ethyl cellulose, Eudragit RL and Eudragit RS types, a mixture of Eudragit RL and Eudragit RS. The coating is preferably present in an amount of about, preferably 10 % to 50 % by weight (page 4: [0039]). Thombre, A. G. teach that for tablet dosage form, it can further include excipients, i.e. microcrystalline cellulose; and a disintegrating agent, i.e. corn starch, potato starch (page 7: [0065]).

Finding of prima facie obviousness Rational and Motivation

(MPEP 2142-2143)

It would have been obvious to one of ordinary skill in the art at the time of the

instant invention to combine the teaching of Katzhendler et al. with Gorham et al. and Thombre, A. G. to arrive at the instant invention.

One of ordinary skill in the art would have been motivated to prepare a carbamazepine (carbazepine) derivative dosage form using MHD as taught by Katzhendler et al. as a carbazepine derivative suitable for use in the disclosed dosage form. Optimization of the type and amount of HPMC result in composition with the desired release profile as discussed in greater detail above, which can be used to prepare a once daily dosage form. The amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ and reasonably would expect success.

One of ordinary skill also would have been motivated to formulate the MHD into a known controlled release dosage because the advantage of a controlled release form is that relatively high local concentration of the active in the gastrointestinal tract are avoided, due to a controlled, gradual distribution of the active throughout the gastrointestinal tract and stomach, as taught by prior art.

With respect to the particle size of 10, 11- dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide, Katzhendler et al. teaches that smaller particles of the poorly water soluble active ingredients results in enhanced solubility. Electron micrographs of various formulations are presented in figures 2 and 3. An artisan or ordinary skill in the art would have optimized the size of the particles to provide enhanced solubility.

Therefore, from the teaching of the references, the invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference.

Conclusion

No claims are allowed.

Contact Information

Any inquiry concerning this communication from the Examiner should direct to Helen Mei-Ping Chui whose telephone number is 571-272-9078. The examiner can normally be reached on Monday-Thursday (7:30 am – 5:00 pm). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where the application or proceeding is assigned is 571-273-8300.

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